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(21) International Application Number: PCT/EP00/03838 (22) International Filing Date: 27 April 2000 (27.04.00) (30) Priority Data: 99108808.9 4 May 1999 (04.05.99) EP (71) Applicant (for all designated States except US): BYK GULDEN LOMBERG CHEMISCHE FABRIK GMBH [DE/DE]; Byk-Gulden-Str. 2, D-78467 Konstanz (DE). (72) Inventor: AMSCHLER, Hermann (deceased). (72) Inventors (for all designated States except CA US): BEUME, Rolf; Bohlstrasse 13, D-78465 Konstanz (DE). HÄFNER, Dietrich; Beethovenstrasse 5, D-78464 Konstanz (DE). SCHUDT, Christian; Schützenstrasse 20, D-78462 Konstanz (DE). HATZELMANN, Armin; Alter Wall 3, D-78467 Konstanz (DE). (72) Inventor; and (75) Inventor/Applicant (for US only): KILIAN, Ulrich [DE/DE]; Am Dachsberg 18, D-78479 Reichenau (DE).		(74) Common Representative: BYK GULDEN LOMBERG CHEMISCHE FABRIK GMBH; Byk-Gulden-Str. 2, D-78467 Konstanz (DE). (81) Designated States: AE, AL, AU, BA, BG, BR, CA, CN, CZ, EE, GE, HR, HU, ID, IL, IN, JP, KR, LT, LV, MK, MX, NO, NZ, PL, RO, SG, SI, SK, TR, UA, US, VN, YU, ZA, ZW, Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: SYNERGISTIC COMBINATION COMPRISING ROFLUMILAST AND A PDE-3 INHIBITOR (57) Abstract The invention relates to the combined use of the PDE4 inhibitor N- (3,5-dichloropyrid-4-yl)- 3-cyclopropylmethoxy- 4-difluoromethoxybenzamide, its pharmacologically tolerable salts or its N- oxide with a PDE3 inhibitor for the treatment of certain disease conditions such as, for example, acute or chronic obstructions of the bronchi.		

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SYNERGISTIC COMBINATION COMPRISING ROFLUMILAST AND A PDE-3 INHIBITOR

Field of application of the invention

The invention relates to the combination of N-(3,5-dichloropyrid-4-yl)-3-cyclopropylmethoxy-4-difluoromethoxybenzamide, its pharmacologically tolerable salts or its N-oxide with known active compounds from the class of PDE3 inhibitors for therapeutic purposes.

Known technical background

The substances used in the combination according to the invention are, on the one hand, N-(3,5-dichloropyrid-4-yl)-3-cyclopropylmethoxy-4-difluoromethoxybenzamide, its pharmacologically tolerable salts or its N-oxide [= N-(3,5-dichloro-1-oxypyrid-4-yl)-3-cyclopropylmethoxy-4-difluoromethoxybenzamide], all of them PDE4 inhibitors, which are described in the international application WO 95/01338 and, on the other hand, known active compounds from the class of PDE3 inhibitors.

Cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) are ubiquitous intracellular second messengers which are involved in many biological processes which are induced by a huge variety of extracellular stimulants. The inactivation (metabolization) of cAMP and cGMP is effected by enzymes of the cyclic nucleotide phosphodiesterase (PDE) type. At least nine different families of PDE isoenzymes have meanwhile been identified (PDE1 to PDE9).

The PDE3 and PDE4 isoenzyme families caused particular interest; a definitive role in the inactivation of cAMP is ascribed to both. Inhibitors of these isoenzymes exhibit actions on the airways, on the peripheral blood pressure, on the central nervous system (e.g. increase in respiratory rates) and anti-inflammatory actions.

The effect on the airways is essentially ascribed to the inhibition of PDE3 and, to a minor extent, also to the inhibition of PDE4. The effects on the blood pressure is regarded as mediated by PDE3, while the anti-inflammatory action and the action on the central nervous system are assigned to the inhibition of PDE4.

The combined use of the PDE4 inhibitor N-(3,5-dichloropyrid-4-yl)-3-cyclopropylmethoxy-4-difluoromethoxybenzamide, its pharmacologically tolerable salts or its N-oxide with a PDE3 inhibitor in the sense according to the invention has still not been described in the prior art.

Subject of the invention

The invention relates to the combined use of N-(3,5-dichloropyrid-4-yl)-3-cyclopropylmethoxy-4-difluoromethoxybenzamide, its pharmacologically tolerable salts or its N-oxide with a PDE3 inhibitor in the treatment of disease conditions which are based on acute or chronic obstruction of vessels and/or bronchi and/or on acute or chronic inflammation.

The preparation of N-(3,5-dichloropyrid-4-yl)-3-cyclopropylmethoxy-4-difluoromethoxybenzamide, its pharmacologically tolerable salts and its N-oxide and the use of these compounds as phosphodiesterase (PDE) 4 inhibitors is described in the international application WO 95/01338.

Pharmacologically tolerable salts of N-(3,5-dichloropyrid-4-yl)-3-cyclopropylmethoxy-4-difluoromethoxybenzamide which may be mentioned are, for example, water-soluble and water-insoluble acid addition salts with acids such as, for example, hydrochloric acid, hydrobromic acid, phosphoric acid, nitric acid, sulfuric acid, acetic acid, citric acid, D-gluconic acid, benzoic acid, 2-(4-hydroxybenzoyl)benzoic acid, butyric acid, sulfosalicylic acid, maleic acid, lauric acid, malic acid, fumaric acid, succinic acid, oxalic acid, tartaric acid, embonic acid, stearic acid, toluenesulfonic acid, methanesulfonic acid or 3-hydroxy-2-naphthoic acid, the acids being employed in salt preparation - depending on whether it is a mono- or polybasic acid and depending on which salt is desired - in an equimolar quantitative ratio or one differing therefrom.

PDE3 inhibitors which can be employed according to the invention and which may be mentioned by way of example are those described or claimed in the following patents and patent applications: EP 0 653 426, EP 0 294 647, EP 0 357 788, EP 0 220 044, EP 0 326 307, EP 0 207 500, EP 0 406 958, EP 0 150 937, EP 0 075 463, EP 0 272 914, EP 0 112 987, US 4,963,561, US 5,141,931, WO 96/15117, DE 28 25 048, DE 27 27 481, DE 28 47 621, DE 30 44 568, DE 28 37 161 and DE 30 21 792.

The following PDE3 inhibitors are to be emphasized here: UK-1745, (-)-(R)-NSP-307, EMD-57033, WIN-62582, WIN-63291, NSP-307, NSP-306, CI-930, SKF-95654, KF-15232, MS-857, REVIZINONE, CI-LOSTAMIDE, AMIPIZONE, SIGUAZODAN, CARBAZERAN, BEMORADAN and MOTAPIZONE. MILRINONE, ENOXIMONE and PIMOPENDAN are particularly to be emphasized.

As a result of simultaneous inhibition of the two underlying metabolism routes (PDE3 and PDE4), a relative increase in the intracellular concentration of cyclic adenosine monophosphate can occur.

The biological effects of the combination following therefrom are not inevitably additive or even super-additive on cellular model systems. Surprisingly, in anesthetized, spontaneously breathing guinea-pigs

treated with histamine, after administration of the combination of N-(3,5-dichloropyrid-4-yl)-3-cyclopropylmethoxy-4-difluoromethoxybenzamide with a PDE3 inhibitor a superadditive synergistic effect was observed in the inhibition of bronchospasms, while the measurements for the blood pressure and the respiratory rate remained unchanged in comparison with the individual administration of N-(3,5-dichloropyrid-4-yl)-3-cyclopropylmethoxy-4-difluoromethoxybenzamide or of a PDE3 inhibitor.

The unexpected, superadditive increase in the bronchospasmolytic activity on the combined administration of the PDE4 inhibitor N-(3,5-dichloropyrid-4-yl)-3-cyclopropylmethoxy-4-difluoromethoxybenzamide and of a PDE3 inhibitor without an influence thereby being exerted on the blood pressure or the respiratory rate, shows a particular suitability of this combination for the treatment of disease conditions such as, for example, acute, obstructive bronchitis, extrinsic or intrinsic bronchial asthma or COPD.

As a result of the combination according to the invention of N-(3,5-dichloropyrid-4-yl)-3-cyclopropylmethoxy-4-difluoromethoxybenzamide, its pharmacologically tolerable salts or its N-oxide with a PDE3 inhibitor, the individual components can be used in concentrations which on their own are not sufficiently active or not active at all. By means of this, side-effects of the individual components which would occur in the intrinsically active concentrations of N-(3,5-dichloropyrid-4-yl)-3-cyclopropylmethoxy-4-difluoromethoxybenzamide, its pharmacologically tolerable salts, its N-oxide or the PDE3 inhibitor on sole administration, are avoided by the lower concentration in the combination.

"Combined use" within the meaning of the present invention is to be understood as meaning that the individual components can be administered simultaneously in a manner which is known and customary per se [in the form of a combination medicament (as fixed or free combination)], more or less simultaneously (from one or separate pack units) or successively (directly one after the other or else also with a relatively great time interval).

In the case of more or less simultaneous administration of the individual components from separate pack units and in the case of the administration of the individual components which takes place successively, if desired a different administration form can be chosen. For example, one component can be administered by inhalation, while the other component is administered by infusion or orally.

The dose of the active compounds is of an order of magnitude customary for the dose of the individual components, it being possible, on account of the mutually positively influencing and increasing individual actions, to lower the respective doses compared with the norm on the combined administration of the active compounds. Exemplary doses for the PDE4 inhibitor N-(3,5-dichloropyrid-4-yl)-3-cyclopropylmethoxy-4-difluoromethoxybenzamide and N-(3,5-dichloro-1-oxypyrid-4-yl)-3-cyclopropylmethoxy-4-difluoromethoxybenzamide which can be mentioned are, in the case of oral administration, a daily dose

of 2µg/kg to approximately 20µg/kg, if appropriate in the form of a number, preferably 1 to 3, individual doses.

In the case of parenteral treatment, similar or (in particular in the case of intravenous administration of the active compound), as a rule, lower doses can be used.

The dose in the case of PDE3 inhibitors is typically in a range from 0.1 to 25 mg/kg per day.

It is known to the person skilled in the art that the optimal dose of an active compound or of an active compound combination can vary as a function of the body weight, the age and the general state of the patient, and his response behavior to the active compound or the active compound combination.

Any person skilled in the art can easily fix the optimal dose and manner of administration of the active compounds necessary in each case on the basis of his/her expert knowledge.

As medicaments, the compounds according to the invention (= active compounds) are either employed as such, or preferably are mixed with suitable pharmaceutical auxiliaries or carriers, e. g. in the form of tablets, coated tablets, capsules, emulsions, suspensions or solutions, whereby the active compounds content is advantageously between 0.1 and 95% and whereby through appropriate choice of the employed pharmaceutical auxiliaries and carriers a galenic formulation can be achieved, which is exactly adapted to the active compounds and/or the desired time of effectiveness.

The person skilled in the art is familiar with auxiliaries which are suitable for the desired pharmaceutical formulations on account of his expert knowledge. In addition to solvents, gel formers, tablet auxiliaries and other active compound excipients, for example antioxidants, dispersants, emulsifiers, preservatives, solubilizers or permeation promoters, can be used.

Claims

1. N-(3,5-dichloropyrid-4-yl)-3-cyclopropylmethoxy-4-difluoromethoxybenzamide, its pharmacologically tolerable salts or its N-oxide combined with a PDE3 inhibitor for use in the therapeutic treatment of disease conditions which are based on acute or chronic obstruction of vessels and/or bronchi and/or on acute or chronic inflammation.
2. The combination as claimed in claim 1, wherein the PDE3 inhibitor is ENOXIMONE, MILRINONE, MILRINONE lactate or PIMOPENDAN.
3. The combination as claimed in claim 1 or 2, wherein the disease conditions are an acute or chronic obstruction of vessels and/or bronchi.
4. The combination as claimed in claim 1 or 2, wherein the disease conditions are an acute or chronic inflammation.
5. Medicaments containing N-(3,5-dichloropyrid-4-yl)-3-cyclopropylmethoxy-4-difluoromethoxybenzamide, its pharmacologically tolerable salts or its N-oxide and a PDE3 inhibitor as a fixed or free combination together with the usual pharmaceutical auxiliaries and/or excipients for use in the therapeutic treatment of disease conditions which are based on acute or chronic obstruction of vessels and/or bronchi and/or on acute or chronic inflammation.
6. Medicaments according to claim 5, characterized in that the active compounds N-(3,5-dichloropyrid-4-yl)-3-cyclopropylmethoxy-4-difluoromethoxybenzamide, its pharmacologically tolerable salts or its N-oxide and a PDE3 inhibitor are readily mixed in a fixed combination for simultaneous administration.
7. Medicaments according to claim 5, characterized in that the active compounds N-(3,5-dichloropyrid-4-yl)-3-cyclopropylmethoxy-4-difluoromethoxybenzamide, its pharmacologically tolerable salts or its N-oxide and a PDE3 inhibitor are present separated from each other in one pack unit for simultaneous, more or less simultaneous or successive administration.
8. Medicaments according to one of the claims 5, 6 or 7, wherein the PDE3 inhibitor is ENOXIMONE, MILRINONE, MILRINONE lactate or PIMOPENDAN.
9. A commercial pharmaceutical product, consisting of a customary secondary pack, a primary pack containing the medicament and, optionally a pack insert, the medicament containing as ac-

tive compound N-(3,5-dichloropyrid-4-yl)-3-cyclopropylmethoxy-4-difluoromethoxybenzamide, a pharmacologically tolerable salt or the N-oxide thereof characterized in that on the secondary pack and/or on the pack insert is indicated that N-(3,5-dichloropyrid-4-yl)-3-cyclopropylmethoxy-4-difluoromethoxybenzamide, the pharmacologically tolerable salt or the N-oxide thereof can be used in combination with a PDE3 inhibitor in the therapeutic treatment of disease conditions which are based on acute or chronic obstruction of vessels and/or bronchi and/or on acute or chronic inflammation.

10. A commercial pharmaceutical product, consisting of a customary secondary pack, a primary pack containing the medicament and, optionally a pack insert, the medicament containing as active compound a PDE3 inhibitor characterized in that on the secondary pack and/or on the pack insert is indicated that the PDE3 inhibitor can be used in combination with N-(3,5-dichloropyrid-4-yl)-3-cyclopropylmethoxy-4-difluoromethoxybenzamide, a pharmacologically tolerable salt or the N-oxide thereof in the therapeutic treatment of disease conditions which are based on acute or chronic obstruction of vessels and/or bronchi and/or on acute or chronic inflammation.

INTERNATIONAL SEARCH REPORT

International Application No.
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/44 A61K31/415

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

BIOSIS, EPO-Internal, CHEM ABS Data, CANCERLIT, MEDLINE, EMBASE, PAJ, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JOHNSON-MILLS, KAREN ET AL: "Effect of CI- 930 (3-(2H)-pyridazinone-4,5-dihydro-6-(4-(1H- imidazolyl) phenyl)-5-methyl-monohydrochloride) and rolipram on human coronary artery smooth muscle cell proliferation." BIOCHEMICAL PHARMACOLOGY, (OCT. 15, 1998) VOL. 56, NO. 8, PP. 1065-1073., XP000874778 page 1072, column 1, paragraph 5 -column 2, paragraph 1	1-4
A	EP 0 435 811 A (ALMIRALL LAB) 3 July 1991 (1991-07-03) page 4, line 36 - line 43	1-4

☐ Further documents are listed in the continuation of box C.

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Information on patent family members

International Application No

PCT/EP 00/03838

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